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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/072,611	02/08/2002	Brian Leyland-Jones	3298.1001-000	1456

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EXAMINER

CHEU, CHANGHWA J

ART UNIT	PAPER NUMBER
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1641

DATE MAILED: 03/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/072,611

Applicant(s)

LEYLAND-JONES, BRIAN

Examiner

Jacob Cheu

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 28 January 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-4,6-29,31-53 and 57-63 is/are pending in the application.
- 4a) Of the above claim(s) 31-50,52,53 and 57 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4,6-29,51 and 58-63 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

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### DETAILED ACTION

Applicant's amendment filed on 1/28/2005 has been received and entered into record and considered.

The following information provided in the amendment affects the instant application:

1. Claims 5, 30 and 54-56 are cancelled.
2. Claims 58-63 are added to the instant application.
3. Currently claims 1-4, 6-29, 51, 58-63 are under examination. Claims 31-50, 52-53 and 57 are withdrawn from further consideration.

### *Claim Rejections - 35 USC § 102*

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-4, 26-29, 51, 58-63 are rejected under 35 U.S.C. 102(b) as being anticipated by Desta et al. (Clinical Pharmacology and Therapeutics 1999 65: 10-20).

Desta et al. teach a method of evaluating the effect of antibiotics clarithromycin on the metabolism of pimozone on individuals suffered with Gilles de la Tourette's (See abstract). Desta et al. teach administering to an individual a probe substrate, i.e. clarithromycin and pimozone and detecting the metabolite from the blood samples (not a breath sample) by HPLC (See Materials and Methods). Desta et al. also teach individualize a selected safe and therapeutically effective drug treatment dosing regime for said individual, such as the safe concentration of pimozone, monitoring electrocardiogram during dosage changes or during administration of drugs (See Discussion, particularly page 19, left column, second paragraph).

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With respect to claims 2-4, Desta et al. use pharmacokinetic analysis, including concentration-time curve, terminal half-life, clearance and volume distribution, peak and ratio, to measure the metabolites in the plasma from the individuals dosed with the pimozone, antibiotics or both. (See Methods; Data analysis; Figures 1-3 )

With respect to claims 26-29, the metabolic enzymes involving in the metabolisms are CYP2D6 and CYP3A. (See abstract; Introduction)

With respect to claims 51 and 58, Wainer et al. teach using two substrates, i.e. clarithromycin and pimozone, to study the enzymatic influence (CYP2D6 and CYP3A), in an individual (See Abstract; page 18, right column, second and third paragraph).

With respect to claims 59-61, Wainer et al. teach treat the individual with a single 6-mg oral dose of a probe substrate, i.e. pimozone, after 5 days of pretreatment with oral clarithromycin, and then compare the pre- and post- compound exposure phenotypes to evaluate the individual's drug metabolizing ability (See Figure 1-3; Table I-II).

3. Claims 1-4, 6-10, 14-15, 25-28, 51 and 62-63 are rejected under 35 U.S.C. 102(b) as being anticipated by Wainer et al. (US 5830672).

Wainer et al. teach a method of characterizing a metabolic phenotype of an individual by administering a probe substrate, i.e. coffee, to an individual, and measuring the biological sample, e.g. urine (not a breath sample), from the individual (See Summary of Invention; claims 1-5). Wainer et al. also teach that using the metabolic phenotype information to individualize therapy of drugs for treatment dosing regime for the individual (See Col. 2, line 5-10, 45-49; claim 5).

With respect to claims 2-4, Wainer et al. teach measuring the ratio of two metabolites, i.e. AAMU and AFMU, and the molar ratio below about 1.80 is indicative of low acetylation phenotype of said individual (See claims 1 and 5).

With respect to claims 6-10, Wainer et al. teach that using caffeine metabolite antibodies, e.g. polyclonal or monoclonal antibodies, to detect the caffeine metabolites in the urine sample (See Example II and III).

With respect to claims 14-15, Wainer et al. teach using a ligand binding assay, i.e. ELISA, to detect the metabolites (See Example II and III).

With respect to claims 25-28, the ELISA assay taught by Wainer et al. is a quantitative assay based on enzyme recognizing binding, e.g. horse peroxidase (See claims 9-10). The metabolic pathway involved with the caffeine is the N-acetyltransferase-2 (NAT-2) (See Abstract).

With respect to claims 62-63, Wainer et al. teach using signal peak height and urine samples from the treated individuals to individualize a safe and therapeutic drug dosing regimen (See claims 1, 5 and 9; Example I-III).

4. Claims 1-4, 62-63 are rejected under 35 U.S.C. 102(b) as being anticipated by Ratain et al. (Cancer Res 1993, vol. 53, page 2204).

Ratain et al. teach a method of metabolic phenotyping to individualize amonafide dosage. Ratain et al. teach using the caffeine as the probe substrate and measure the plasma samples of cancer patients for acetylator phenotype (See Materials and Methods). Ratain et al. teach that characterizing the therapeutical dosage regimen of amonafide by the metabolic phenotypes, such as slow, intermediate, and fast metabolizing of amonafide capabilities (See Results; Figures 1-2). Ratain et al. teach individualizing safety and therapeutic treatment based on this phenotype, where the initial dose levels for slow, intermediate, and fast acetylators were 375, 300 or 250 mg/m<sup>2</sup>, respectively (See Amonafide Dosing, page 2304).

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With respect to claims 2-4, Ratain et al. also teach using the HPLC to measure the molar ratio of “urinary concentration of an acetylated (AAMU) and nonacetylated (1X) metabolites” (See Acetylator Phenotyping, page 2305). The samples are withdrawn from the patients’ plasma (See Materials and Methods).

***Claim Rejections - 35 USC § 103***

5. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wainer et al. (US 5830672), in view of Cubicciotti et al. (US 6287765).

Wainer et al. reference has been discussed but does not explicitly teach using aptamer or receptor for drug metabolites study. Cubicciotti et al. reveal that it is known in the art that aptamer or receptor would bind to the therapeutic metabolic target, and therefore can be detected by modified ELISA increase sensitivity, cost-effectiveness and reproducibility. (See example 21 and example 22) Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided Wainer et al. with the affinity complexation agent as taught by Cubicciotti et al. since it is known in the pharmaceutical practice to detect the binding of receptor or aptamer to the target compound to increase sensitivity, cost-effectiveness and reproducibility.

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7. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wainer in view of Beste et al. (PNAS 1999 96: 1898-1903)

Wainer reference has been discussed but does not explicitly teach using anticalin for binding assay. Beste et al. teach that using lipocalin as an alternative for conventional antibodies for ligand binding assay. (See abstract) Beste et al. reveal that conventional antibodies have certain disadvantages such as larger molecules not easy to manipulate, or two polypeptide chains complicate cloning procedure. (page 1898, left column, first paragraph) Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided Desta and Wainer et al. with the alternative anticalin as taught by Beste et al. for convenience and economy in detecting the target molecules.

8. Claim 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wainer in view of Pronovost et al. (US 5786220).

Desta and Wainer references have been discussed but do not explicitly teach using dipstick immunoassay to detect metabolites in a sample. Pronovost et al. teach using dipstick for quick detecting the presence of metabolites in patient sample. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided Desta and Wainer et al. with dipstick immunoassay as taught by Pronovost et al. to detect metabolites in a patient sample in a time-saving manner.

9. Claims 18-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wainer et al., in view of Rabbany et al. (Critical Reviews in Biomedical Engineering 1994 22: 307-346).

Wainer et al. reference has been discussed but does not explicitly teach using various biosensors for detection purposes. Rabbany et al. review the immunosensors in applications to the detection of analytes in samples, including optical, piezoelectric, electrochemical sensors. (See page 320-340) Therefore, it would have been obvious to

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one of ordinary skill in the art at the time the invention was made to have provided Wainer et al. with alternative biosensors for detection of analytes as taught by Rhbbany et al. since it is well-known in the art to use the different biosensors to detect target molecules in the sample, and choosing optimal one merely involves routine skill in the art.

10. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wainer, in view of Wang et al. (Anal. Chem. 1997 69: 5200-5202).

Wainer et al. reference have discussed but does not explicitly teach using quartz crystal microbalance (QCM) to detect peptide nucleic acids. Wang et al. teach using QCM biosensor to detect DNA-protein complex in a biological sample. (See abstract, page 5200, right column, second paragraph) Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided Wainer et al. with the aid of QCM biosensor as taught by Wang et al. for the detection of aptamer complex, e.g. DNA-protein-metabolites, in the patient plasma sample to determine the phenotype of the patient in response to the treatment of therapeutics because it is well-known in the art to use the different biosensors to detect target molecules in the sample, and choosing optimal one merely involves routine skill in the art.

### *Response to Applicant's Arguments*

11. The rejections of claims 1-4, 26-29, 51, 58-63 under 35 U.S.C. 102(b) as being anticipated by Desta et al. are maintained.

Applicant argues that the newly amended feature of characterizing metabolic phenotype of said individual based on detected metabolites "to individualize a selected safe and therapeutically effective drug treatment dosing regimen for said individual" is not taught by Desta et al. and the rejections should be withdrawn accordingly (emphasis added).

Applicant's argument has been considered but is not persuasive. In view of Desta et al. reference, at the end Desta et al. stress the importance of individualize a selected safe and therapeutically effective drug treatment dosing regimen. As indicated in this Office Action, Desta et al. also teach individualizing a selected safe and therapeutically effective drug treatment dosing regime for said individual, such as the safe concentration of pimozide, monitoring electrocardiogram during dosage changes or during administration of drugs (See Discussion, particularly page 19, left column, second paragraph). Accordingly, Desta et al. reference encompasses the newly amended feature of "*to individualize a selected safe and therapeutically effective drug treatment dosing regimen for said individual.*"

12. Applicant's arguments with respect to claims 6-25 have been considered but are moot in view of the new ground(s) of rejection.

### ***Conclusion***

13. No claim is allowed.
14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

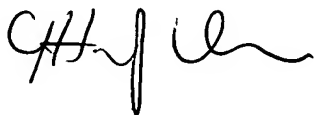
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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-272-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.


Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jacob Cheu  
Examiner



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March 15, 2005

  
LONG V. LE  
SUPERVISORY PATENT EXAMINER  
MARCH 15 2005  
03/17/05